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Review

The Conundrum of Clinical Trials for the Uveitides: Appropriate Outcome Measures for One Treatment Used in Several Diseases

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The uveitides consist of >30 diseases characterized by intraocular inflammation. Noninfectious intermediate, posterior, and panuveitides typically are treated with oral corticosteroids and immunosuppression, with a similar treatment approach for most diseases. Because these uveitides collectively are considered a rare disease, single-disease trials are difficult to impractical to recruit for, and most trials have included several different diseases for a given protocol treatment. However, measures of uveitis activity are disease specific, resulting in challenges for trial outcome measures. Several trials of investigational immunosuppressive drugs or biologic drugs have not demonstrated efficacy, but design problems with the outcome measures have limited the ability to interpret the results. Successful trials have included diseases for which a single uveitis activity measure suffices or a composite measure of uveitis activity is used. One potential solution to this problem is the use of a single, clinically relevant outcome, successful corticosteroid sparing, defined as inactive uveitis with a prednisone dose ≤7.5 mg/day coupled with disease-specific guidelines for determining inactive disease. The clinical relevance of this outcome is that active uveitis is associated with increased risks of visual impairment and blindness, and that prednisone doses ≤7.5 mg/day have a minimal risk of corticosteroid side effects. The consequence of this approach is that trial visits require a core set of measures for all participants and a disease-specific set of measures, both clinical and imaging, to assess uveitis activity. This approach is being used in the Adalimumab Versus Conventional Immunosuppression (ADVISE) Trial.

clinical trials; outcome measures; uveitis

Abbreviations: ADVISE, Adalimumab Versus Conventional Immunosuppression; CI, confidence interval; FAST, First-Line Antimetabolites as Steroid-Sparing Treatment Uveitis; FDA, Food and Drug Administration; HR, hazard ratio; MUST, Multicenter Uveitis Steroid Treatment; NIIPPU, noninfectious intermediate; OCT, optical coherence tomography/tomogram; OR, odds ratio.

INTRODUCTION

The uveitides consist of >30 distinct diseases characterized by intraocular inflammation (1, 2). Traditionally, they are grouped anatomically by the primary site of inflammation determined clinically as anterior, intermediate, posterior, or panuveitides (1, 2). Anterior uveitides are characterized by inflammation in the anterior chamber of the eye; intermediate uveitides in the vitreous; posterior uveitides in the retina, retinal pigment epithelium, or choroid; and panuveitides by inflammation involving all parts of the eye without 1 area predominating (1, 2). Uveitides also are characterized as infectious or noninfectious. The estimated prevalence of uveitis in the United States varies from 115 to 204 cases per 100,000 people, and the incidence varies from 17 to 54 cases per 100,000 people per year (3–5). The large majority of uveitides are classified as anterior, and noninfectious intermediate, posterior, and panuveitides (NIIPPU) collectively are considered a rare disease by the US Food and Drug Administration (FDA) (6). Although less frequent than anterior uveitides, the rates visual loss with intermediate, posterior, and panuveitides are much higher than with anterior uveitides (7, 8). The uveitides collectively are the fifth or sixth cause of blindness in the United States, and the cost of uveitis care is estimated to be similar to that of diabetic retinopathy (9, 10). The most common complication

of uveitis causing visual loss is macular edema, which is vascular leakage resulting in accumulation of intraretinal fluid in the macula; it affects approximately 50% of patients with intermediate, posterior, or panuveitides (11).

Infectious uveitides are treated with antimicrobial agents, often supplemented by adjunctive topical or oral corticosteroid therapy to minimize structural complications and damage. Noninfectious anterior uveitides typically are treated with topical corticosteroids, although children with juvenile idiopathic arthritis–associated chronic anterior uveitis may require immunosuppression for long-term management and corticosteroid sparing (12–15). Topical corticosteroids are ineffective for intermediate, posterior, and panuveitides, most of which are chronic diseases and typically are treated with oral corticosteroids and immunosuppressive drugs (13–15). The immunosuppressive drugs used include antimetabolites (namely, azathioprine, methotrexate, and mycophenolate) and calcineurin inhibitors (namely, cyclosporine and tacrolimus) (14, 15). Alkylating agents (e.g., cyclophosphamide, chlorambucil) have been reported to be highly effective but now are used infrequently because of concerns about late cancers developing with these drugs (14–18). More recently, biologic agents, particularly anti–TNF-α monoclonal antibodies, have been investigated as uveitis treatments (19–22). Cohort studies using time-updated analyses of several posterior or panuveitides have suggested approximately 80% to 85% success for this approach in terms of prevention of structural complications and preservation of vision (23–26). Based on these data, the approach for most NIIPPU needing treatment has been similar regardless of the specific disease (15). The exception is Behçet disease uveitis, which appears to have better long-term outcomes with early use of anti–TNF-α biologic drugs (22, 27).

Important management issues in the use of oral corticosteroids and immunosuppression for the uveitides include adequate control of the inflammation and successful tapering of oral corticosteroids to a dose at which long-term use has no to minimal side effects (prednisone ≤7.5 mg/day). Results of cohort studies in which time-updated analyses were used have suggested that patients with inactive uveitis do better in the long term than do those with active inflammation; active inflammation appears to approximately double the risk of visual impairment (i.e., visual acuity worse than 20/40) and triple the risk of blindness (i.e., visual acuity 20/200 or worse) (28, 29). In randomized clinical trials and cohort studies, long-term use of prednisone doses ≤7.5 mg/day had minimal side effects (30–33). In the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study, corticosteroid use at high doses (60 mg/day) followed by tapering to ≤7.5 mg/day with follow-up for 7 years was associated with no increase in systemic corticosteroid side effects (vs. intraocular corticosteroids alone) other than a greater use of antibiotics for infection (32, 33). Although this approach is effective, single-agent immunosuppression with a conventional (i.e., nonbiologic), nonalkylating-agent drug is successful at controlling the inflammation and permitting tapering prednisone to a "safe" dose in approximately 40%–60% of cases (34–40), and in approximately 25% of cases, combination immunosuppression (i.e., 2 immunosuppressive drugs) is needed (41). Therefore, there is ongoing interest in the development of additional drugs to treat NIIPPU. There also has been ongoing work on regionally administered corticosteroids—periocular, intravitreal, or more recently, suprachoroidal approaches, which essentially eliminate the risk of systemic side effects, but which may increase the risks of corticosteroid-related ocular side effects (42–46). These regionally administered drugs may be either short-acting (e.g., ≤6 months' duration) or long-acting (≥3 years). Short-acting regional corticosteroid injections (typically 1 or 2) also are used as adjunctive therapy for control of uveitic macular edema (11).

Intraocular inflammation severity can be assessed in the anterior chamber and vitreous using slit-lamp examination and graded using semiquantitative grading systems, such as those adopted by the Standardization of Uveitis Nomenclature (SUN) Working Group (2). These grading systems have demonstrated reasonable reliability and interobserver agreement (47). However, these grading systems do not adequately evaluate posterior segment inflammation. Posterior segment inflammation is evaluated using chorioretinal imaging techniques such as optical coherence tomography (OCT) for exudative retinal detachments and macular edema, fundus autofluorescence for choroidal inflammatory lesions, and fluorescein angiography for retinal vascular inflammation (e.g., retinal vasculitis) (48–53). For posterior segment inflammation, the imaging techniques that are appropriate are disease specific, and although active versus inactive uveitis can be determined, neither quantitative nor semiquantitative grading systems have been developed and used widely as yet.

UVEITIS CLINICAL TRIALS

Trials of topical corticosteroids for noninfectious anterior uveitides have been successful in evaluating these drugs (54, 55), in part because of the availability of a standardized, reliably graded, and clinically meaningful outcome measure, namely anterior chamber cells (2, 47). The measure is applicable to all of the anterior uveitides, thus, participants with several diseases may be enrolled in trials (2), permitting more rapid recruitment. Appropriate outcomes for these trials include grade 0 cells (i.e., inactive disease) and a 2-step improvement in the anterior chamber cells on a semiquantitative scale, such as the SUN scale for grading anterior chamber cells (2). The 2-step threshold is used because it is considered to exceed the interobserver variability of the semiquantitative scales used to assess anterior chamber cells (2, 47).

However, trials of treatments NIIPPU have encountered difficulties due to the lack of a single, universally applicable, and clinically meaningful outcome measure of inflammation. Patients with several diseases typically are enrolled in these trials and, with a few exceptions, these are not disease-specific trials. Reasons for this approach include 1) NIIPPU collectively are a rare disease, making recruitment of adequate numbers of participants for a single disease trial in a reasonable time logistically difficult to impossible; and 2) these diseases typically are treated in a similar

manner, using the same drugs and treatment algorithms (13–15) with little evidence of differential treatment response by disease (except possibly Behçet disease uveitis) (22). However, this "lumping" approach has created problems in the definition of the primary outcome for these trials.

Outcomes for trials of new agents for uveitis typically are either visual acuity or uveitis control, and the US FDA considers these appropriate outcomes (Wiley Chambers, US Food and Drug Administration, personal communication, 2019). Uveitis control can either be inactive disease or improvement, typically defined as a ≥ 2-step improvement on the semiquantitative grading schema. For trials in which relapse is used as a primary outcome, worsening typically represents a ≥2-step increase in inflammation, but over time, some more complex definitions of relapse have been developed in some trials.

One of the first trials directed at evaluating a new treatment for NIIPPU was the Chronic Uveitis Evaluation of the Intravitreal Dexamethasone Implant (HURON) Trial (Table 1), in which patients were randomly assigned to either 1 of 2 doses of the dexamethasone intravitreal implant (350 μg or 700 μg) or to sham injection. Enrollment criteria included that patients had ≥1+ vitreous haze on examination using the semiquantitative National Eye Institute vitreous haze grading system, and the primary outcome was grade 0 vitreous haze (i.e., inactive disease). Both doses of the dexamethasone intravitreal implant were more effective than sham injection (700 μg dose vs. sham: 47% vs. 12%, $P < 0.001$; and 350 μg dose vs. sham: 36% vs. 12%, $P < 0.001$) (42). As a result of this trial, the FDA approved the 700-μg dose (Ozurdex; Allergan, Inc., Irvine California) for a uveitis indication. This trial was successful in part because 81% of the enrolled participants had intermediate uveitis (inflammation primarily in the vitreous), for which vitreous haze is a good measure of ocular inflammation. However, trials enrolling participants with several NIIPPU diseases have fared less well.

Voclosporin (experimental drug Lx211), a calcineurin inhibitor, was investigated for a uveitis indication. Three trials (Table 1) were performed: 1 each in active NIIPPU with ≥2+ vitreous haze (Lx211–01), in inactive NIIPPU (Lx211–02); and in anterior uveitides (Lx211–03). The primary outcome of the first trial was mean change in vitreous haze; for the second trial, it was uveitis relapse (defined as ≥2-step increase in anterior chamber or vitreous inflammation or a 0.3 $\log_{10}$ decrease in visual acuity); and for the third trial, the primary outcome was mean change in anterior chamber cells. All the trials used a 1:2:2:2 randomization to placebo or to 1 of 2 doses of voclosporin (0.2 mg/kg, 0.4 mg/kg, or 0.6 mg/kg) (57, 58). Although there was some suggestion of modest efficacy at the higher doses (58), in none of the trials was a clinically meaningful primary outcome achieved, and voclosporin never was approved for a uveitis indication. These trials had several problems, including a small number of participants randomly assigned to placebo, which limited the trials' power, but among them was the use of vitreous haze as the sole measure of inflammation in the first 2 trials, while allowing enrollment of participants with diseases for which vitreous haze might not be a good measure of uveitis control.

Secukinumab is a monoclonal antibody to interleukin-17A. It is approved by the FDA for the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis. Secukinumab was evaluated for the treatment of uveitides in 3 trials. The Phase III Study in Refractory Behçet's Disease (SHIELD) Trial enrolled patients with Behçet disease uveitis with ≥2 recurrences in the 6 months prior to randomization, and assigned participants to 1) secukinumab subcutaneously 300 mg every 2 weeks, 2) secukinumab 300 mg every 4 weeks, or 3) placebo. The primary outcome was the reduction in the recurrence rate during the 24-week study period (Table 1). Treatment was added to ongoing immunosuppressive drug treatment at enrollment, and tapering of concomitant corticosteroids and immunosuppression, using clinician discretion, was permitted. The trial did not demonstrate benefit in the primary outcome; the odds ratios (ORs) for recurrences were as follows: secukinumab 300 mg every 2 weeks, 1.4 (95% confidence interval (CI): 0.6, 3.1; and secukinumab 300 mg every 4 weeks, 1.8 (95% CI: 0.8, 4.0). However, the 2 secukinumab treatment groups had a greater decrease in the immunosuppressive medication score (300 mg every 2 weeks, −1.6, $P = 0.10$; 300 mg every 4 weeks, −3.2, $P = 0.05$) than did placebo (−0.5), suggesting possible efficacy that could have been confounded by evaluation of recurrences while permitting differential concomitant medication tapering (59). The Safety and Efficacy of AIN457 in Patients With Active Noninfectious Uveitis (INSURE) Trial (Table 1) enrolled participants with active NIIPPU with ≥2+ vitreous haze, and participants were randomly assigned to 1 of 4 groups: secukinumab 300 mg every 2 weeks, secukinumab 300 mg every 4 weeks, secukinumab 150 mg every 4 weeks, or placebo. Treatment was added to ongoing immunosuppressive drug treatment at enrollment. and tapering of concomitant corticosteroids and immunosuppression, using clinician discretion, was permitted. The trial was stopped early when the results of the other 2 trials were known, but the trial also did not demonstrate any benefit of treatment for the primary outcome. The mean change in vitreous haze scores were as follows: 300 mg every 2 weeks, −1.00; 300 mg every 4 weeks, −1.35; 150 mg every 4 weeks, −0.88; and placebo, −1.13. As in the SHIELD Trial, there was differential use of concomitant immunosuppressive drug medications; the mean change in the immunosuppressive medication score for each of the 3 secukinumab groups was 0, whereas it was +1.83 in the placebo group, a difference that could have confounded the interpretation of the primary result (59). The Safety and Efficacy of AIN457 in Patients With Quiescent Noninfectious Uveitis (ENDURE) Trial enrolled participants with inactive NIIPPU who were assigned to the same 4 treatment groups as in the INSURE Trial (Table 1). Diseases for which either anterior chamber inflammation or vitritis were not characteristic were excluded from the ENDURE Trial. However, no significant differences were demonstrated among the 4 groups in either the time to recurrence or the change in immunosuppressive medication score (59).

The 2 Sirolimus Study Assessing Double-Masked Uveitis Treatment (SAKURA) trials (Table 1) evaluated intravitreal sirolimus as a treatment for NIIPPU. Sirolimus is an immunosuppressive drug that inhibits the enzyme mechanistic

Table 1. Clinical Trials of Noninfectious Uveitides and Uveitic Macular Edema

Trial Name (Reference No.)	Year	No. of Participants	Treatment Groups	Primary Outcome	Outcome Definition	Primary Result
HURON (42)	2011	NIIPPU and vitreous haze >1+ ($n = 229$; 81% with intermediate uveitis)	IVDI 0.7 mg vs. IVDI 0.35 mg vs. sham injection	Grade 0 vitreous haze at week 8	SUN/NEI vitreous haze semiquantitative scoring system	Both doses of IVDI superior to sham injection (47% vs. 36% vs. 12%; $P < 0.001$ for each dose vs. sham)
Lx211–01[a] (57, 58)	2008	Active NIIPPU and ≥2+ vitreous haze ($n = 245$)	Voclosporin vs. placebo	Mean change in vitreous haze	SUN/NEI vitreous haze semiquantitative scoring system	Voclosporin did not meet primary outcome vs. placebo
Lx211–02[a] (57, 58)	2008	Inactive NIIPPU ($n = 263$)	Voclosporin vs. placebo	Relapse uveitis	Increase in vitreous haze or anterior chamber cells by 2 steps or decrease in visual acuity by 0.3 $\log_{10}$ units	Voclosporin did not meet primary outcome vs. placebo
Lx211–03[a] (57, 58)	2008	Active anterior uveitis (anterior chamber cells ≥2+) ($n = 121$)	Voclosporin vs. placebo	Mean change in anterior chamber cells	SUN anterior chamber cells semiquantitative scoring system	Voclosporin did not meet primary outcome vs. placebo
SHIELD Trial (59)	2013	Behçet disease with ≥2 recurrences in 6 months prior to enrollment ($n = 118$)	Sckq2 vs. Sckq4 vs. placebo	Number of recurrences over 24 weeks	Clinician-determined recurrence	Sckq2 and Sckq4 not superior to placebo (for recurrence, OR =1.4 (95% CI: 0.6, 3.1) and 1.8 (95% CI: 0.8, 4.0), respectively)
INSURE Trial (59)	2013	Active NIIPPU ($n = 31$) with ≥2+ vitreous haze	Sckq2 vs. Sckq4 vs. Sck150q4 placebo	Mean change vitreous haze	SUN/NEI vitreous haze semiquantitative scoring system	Sckq2, Scq4, and Sck150q4 not superior to placebo (mean Δ vitreous haze = –1.00 vs. –1.35 vs. –0.88 vs. –1.13)
ENDURE Trial (59)	2013	Inactive NIIPPU ($n = 125$)	Sckq2vs. Sckq4) vs. Sck150q4 vs. placebo	Time to uveitis relapse	Clinician-determined relapse	Sckq2, Sckq4, and Sck150q4 not superior to placebo (no differences in time to relapse and mean Δ ISM score: – 2.55 vs. –2.81 vs. –2.92 vs. –2.31)

Table continues

Table 1. Continued

Trial Name (Reference No.)	Year	No. of Participants	Treatment Groups	Primary Outcome	Outcome Definition	Primary Result
VISUAL I (19)	2016	Active NIIPPU ($n = 217$)	Adalimumab 40 mg every other week vs. placebo	Uveitis relapse	*At 6 weeks*: anterior chamber cells or vitreous haze grades >0.5+; new chorioretinal inflammatory lesions; decrease in visual acuity by ≥15 letters on a logarithmic visual acuity chart *After 6 weeks*: ≥2-step increase in anterior chamber cells or vitreous haze; new inflammatory chorioretinal lesions; decrease in visual acuity by ≥15 letters	Adalimumab superior to placebo (HR = 0.50, 95% CI: 0.36, 0.70; $P < 0.001$)
VISUAL II (20)	2016	Inactive NIIPPU (N = 229)	Adalimumab 40 mg q other week vs. placebo	Uveitis relapse	≥2-step increase in anterior chamber cells or vitreous haze; new inflammatory chorioretinal lesions; decrease in visual acuity by ≥15 letters	Adalimumab superior to placebo (HR = 0.57, 95% CI: 0.39, 0.84; $P = 0.004$)
SAKURA I Trial (60)	2016	NIIPPU with vitreous haze >1+ ($n = 347$)	Intravitreal sirolimus 440 μg vs. 880 μg vs. 44 μg	Grade 0 vitreous haze at 5 months	SUN/NEI vitreous haze semiquantitative scoring system	440 μg superior to 44 μg (22.8% vs. 10.3%; $P = 0.025$); 880 μg not superior to 44 μg (16.4% vs. 10.3%; $P = 0.600$)
SAKURA II Trial (61)	2020	NIPPU with vitreous haze >1+ ($n = 593$)	Intravitreal sirolimus 440 μg vs. 880 μg vs. 44 μg	Grade 0 vitreous haze at 5 months	SUN/NEI vitreous haze semiquantitative scoring system	440 μg not superior to 44 μg (19.1% vs. 17.6%; $P = 0.783$); 880 μg not superior to 44 μg (13.5% vs. 17.6%; $P = 0.485$)

Table continues

Table 1. Continued

Trial Name (Reference No.)	Year	No. of Participants	Treatment Groups	Primary Outcome	Outcome Definition	Primary Result
SYCAMORE (21)	2017	JIA-associated uveitis on methotrexate ($n = 90$)	Adalimumab vs. placebo	Uveitis relapse	≥2-step increase in or persistent (2 consecutive visits) ≥3+ anterior chamber cells on semiquantitative anterior chamber–cells scoring scale or new occurrence or worsening of associated ocular conditions. Associated ocular conditions included 1) disc edema; 2) macular edema; 3) elevated intraocular pressure > 25 mm Hg (despite anti-glaucoma medications); 4) hypotony (intraocular pressure < 6 mm Hg); or 5) ≥15-letter loss of visual acuity on a logarithmic visual acuity chart.	Adalimumab superior to placebo (HR = 0.25, 95% CI: 0.12, 0.49; $P = 0.002$)
MUST Trial & Follow-up Study (32, 33)	2017	Recently (≤60 days) active NIIPPU ($n = 255$)	FAI 0.59 mg vs. oral corticosteroids and immunosuppression	Change in visual acuity from baseline at 7 years	Letters read on logarithmic visual acuity scale	Systemic therapy superior to FAI (mean visual acuity change +1 vs. –6 letters; $P = 0.006$)
EYEGUARD B Trial (63)	2018	Behçet disease uveitis with posterior segment involvement ($n = 83$)	Gevokizumab 60 mg subcutaneously monthly vs. placebo	Time to uveitis relapse	Either ≥2-step increase in or increase to 4+ for anterior chamber cells or vitreous haze or development of retinal infiltrates or acute retinal vasculitis or ≥ 15-letter decrease in visual acuity on a logarithmic visual acuity chart	Gevokizumab not superior to placebo (relapse at 6 months 35% vs. 35%; HR = 0.85, 95% CI: 0.41, 1.77; $P = 0.66$)
Eyepoint Fluocinolone acetonide insert trial (44, 45)	2019	NIIPPU ($n = 129$)	Intravitreal FAI 0.18 mg vs. sham injection	Uveitis relapse at 6 months	≥2-step increase in vitreous haze or ≥ 15-letter decrease in visual acuity on logarithmic visual acuity chart or use of corticosteroids (topical or regional or systemic) and/or systemic immunosuppressive drugs	FAI superior to sham injection (28% vs. 91%; $P < 0.001$)

Table continues

Table 1. Continued

Trial Name (Reference No.)	Year	No. of Participants	Treatment Groups	Primary Outcome	Outcome Definition	Primary Result
SATURN Trial (62)	2019	Active NIIPPU (N = 58)	Subcutaneous sarilumab 200 mg vs. placebo	Treatment success	≥2-step reduction in vitreous haze or prednisone <10 mg/day	Sarilumab not superior to placebo (46.1% vs. 30%; $P = 0.24$)
FAST Trial (83)	2019	NIIPPU ($n = 194$)	Methotrexate 25 mg/week vs. mycophenolate 3 gm/day	Corticosteroid sparing success at 6 months	Inactive disease, topical prednisolone acetate 1% ≤ 2 times/day, and prednisone ≤7.5 mg/day. Inactive disease defined as ≤0.5+ anterior chamber cells and ≤ 0.5+ vitreous haze and no active chorioretinal lesions	Methotrexate noninferior to mycophenolate (OR = 1.5, 95% CI: 0.81, 2.81; $P = 0.20$)
POINT Trial (68)	2019	Uveitic macular edema ($n = 192$)	Periocular TA 40 mg vs. intravitreal TA 4 mg vs. IVDI 0.7 mg	Macular CSFT on optical coherence tomography at 8 weeks	Ratio of CSFT at 8 weeks to baseline CSFT on OCT	Periocular TA inferior to IVTA and to IVDI (CSFT reduction 23% vs. 39% ($P < 0.001$) vs. 46% ($P < 0.001$). IVDI noninferior to IVTA (ratio of reductions 0.88, 99% CI: 0.71, 1.08)
PEACHTREE Trial (46)	2020	Uveitic macular edema ($n = 160$)	Suprachoroidal TA 4 mg vs. sham injection	Visual improvement	≥15-letter improvement on logarithmic visual acuity chart	Suprachoroidal TA superior to sham injection (visual improvement in 47% vs. 16%; $P < 0.001$)

Abbreviations: ADVISE, Adalimumab versus Conventional Immunosuppression; CI, confidence interval; CSFT, central subfield thickness; ENDURE, Safety and Efficacy of AIN457 in Patients With Quiescent Noninfectious Uveitis; EYEGUARD B, A Randomized, Double-Masked, Placebo-Controlled Study of the Efficacy of Gevokizumab in the Treatment of Patients With Behçet's Disease Uveitis (Phase III); FAI, fluocinolone acetonide implant; FAST, First-Line Antimetabolites as Steroid-Sparing Treatment; HR, hazard ratio; HURON, Chronic Uveitis Evaluation of the Intravitreal Dexamethasone Implant; INSURE, Safety and Efficacy of AIN457 in Patients With Active Noninfectious Uveitis; ISM, immunosuppressive medication score; IVDI, intravitreal dexamethasone implant; IVTA, intravitreal triamcinolone acetonide; JIA, juvenile idiopathic arthritis; NEI, National Eye Institute; NIIPPU, noninfectious intermediate, posterior, or panuveitides; OR, odds ratio; PEACHTREE, Suprachoroidal Injection of CLS-TA in Subjects With Macular Edema Associated With Noninfectious Uveitis; POINT, Periocular Versus Intravitreal Corticosteroids for Uveitic Macular Edema; SAKURA, Sirolimus Study Assessing Double-Masked Uveitis Treatment; SATURN, Sarilumab for the Treatment of Posterior Segment Noninfectious Uveitis; Sckq2, secukinumab subcutaneously 300 mg every 2 weeks; Sckq4, secukinumab subcutaneously 300 mg every 4 weeks; Sck150q, secukinumab 150 mg every 4 weeks; SHIELD, Phase III Study in Refractory Behçet's Disease; SUN, Standardization of Uveitis Nomenclature; SYCAMORE, Randomized Controlled Trial of the Clinical Effectiveness, Safety and Cost Effectiveness of Adalimumab in Combination With Methotrexate for the Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis; TA, triamcinolone acetonide; VISUAL I, Efficacy and Safety of Adalimumab in Subjects With Active Uveitis; VISUAL II, Efficacy and Safety of Adalimumab in Subjects With Inactive Uveitis; △, difference.

[a] Voclosporin.

target of rapamycin (mTor). The primary outcome for both trials was grade 0 vitreous haze, and in both trials, participants were randomly assigned into 3 groups based on the sirolimus dose: 440 μg, 880 μg, and the presumably less-effective (and, therefore, theoretically a placebo stand-in) 44-μg dose. The first trial suggested modest efficacy for the 440-μg dose (22.8% vs. 10.3% for the 44 μg dose; $P = 0.025$) (60) but did not demonstrate efficacy for the 880-μg dose. In the second trial, neither of the 2 doses was superior to the 44-μg dose (61), and sirolimus was not approved for a uveitis indication. These trials also permitted randomization of participants with diseases for whom vitreous haze might not be a good measure of activity.

The Sarilumab for the Treatment of Posterior Segment Noninfectious Uveitis (SATURN) Trial (Table 1) evaluated subcutaneous sarilumab, a monoclonal antibody to the interleukin-6 receptor, as a treatment for NIIPPU. The trial was placebo controlled, and the primary outcome was a ≥ 2-step reduction in vitreous haze or a tapering of prednisone to <10 mg/day. Sarilumab did not achieve a significant improvement in the primary outcome (46.1% vs. 30%; $P = 0.24$). Although the small sample size ($n = 58$) increased the likelihood of a type II error, sarilumab demonstrated superiority in some of the secondary outcomes. The visual acuity in the sarilumab group improved by a mean of 8.9 letters but only by 3.6 letters in the placebo group ($P = 0.03$), and macular edema improved by a mean of 46.8 μm in the sarilumab group, whereas it worsened by 2.6 μm in the placebo group ($P = 0.07$) (62). The apparent efficacy on secondary outcomes, but failure in the primary outcome, highlights the potential problem of vitreous haze as a primary outcome for trials permitting enrollment of diseases for which vitreous haze might not be a good measure of activity.

The fluocinolone acetonide insert is a sustained-release implant containing 0.18 mg of fluocinolone acetonide injected intravitreally and designed to release drug over 3 years. In the EyePoint fluocinolone acetonide insert trial, participants with NIIPPU were randomly assigned to either the intravitreal fluocinolone acetonide insert or sham injection. The primary outcome was uveitis relapse at 6 months. For the trial, researchers broadened the definition of relapse from worsening vitreous haze to any of the following: 1) ≥2-step increase in vitreous haze, 2) ≥15-letter decrease in visual acuity measured on a logarithmic visual acuity chart, or 3) use of additional corticosteroids or immunosuppressive drugs. The insert was effective; at 6 months, relapse occurred in 27.5% of patients in the fluocinolone acetonide group versus 90.5% in the sham group ($P < 0.001$) (44). These results led to the FDA approval of the fluocinolone acetonide 0.18-mg insert (Yutiq; EyePoint Pharmaceuticals, Inc., Watertown, Massachusetts) for a uveitis indication. However, the majority of outcome events were not due to an increase in vitreous haze (1.1% in the fluocinolone acetonide insert group and 28.6% in the sham-injection group) but to other reasons ("imputed," in the authors' terminology (44); 26.4% in the fluocinolone acetonide insert group and 61.9% in the sham injection group), highlighting the limitations of the use of vitreous haze as an outcome for trials enrolling participants with diseases other than intermediate uveitides.

Adalimumab (Humira; AbbVie, Inc., Chicago, Illinois) is a monoclonal antibody to TNF-α, administered subcutaneously, and is approved by the FDA for treatment of several immune-mediated diseases, including rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and inflammatory bowel disease. Its use was assessed in 2 clinical trials, Efficacy and Safety of Adalimumab in Subjects With Active Uveitis (VISUAL I) and Efficacy and Safety of Adalimumab in Subjects With Inactive Uveitis (VISUAL II) (Table 1). Participants with NIIPPU and active uveitis were enrolled in VISUAL I, and participants with NIIPPU and inactive uveitis were enrolled in VISUAL II . In both trials, participants were randomly assigned to adalimumab or placebo. In VISUAL I, participants were treated with a standard course of oral corticosteroids, which was then tapered and discontinued. In VISUAL II, participants had oral corticosteroids tapered and discontinued in a standard fashion. In the both trials, the primary outcome was time to uveitis relapse. Because participants with active uveitis, whose uveitis theoretically could fail to respond to the initial treatment regimen, were enrolled in VISUAL I, researchers defined relapse in 2 ways. At 6 weeks, "relapse" was defined as either anterior chamber cells or vitreous haze >0.5+ (i.e., persistent activity) or new chorioretinal inflammatory lesions or a decline in visual acuity of ≥15 letters on a logarithmic visual acuity chart; after 6 weeks, relapse was defined as a ≥ 2-step increase in either anterior chamber cells or vitreous haze or new chorioretinal inflammatory lesions or a decline in visual acuity of ≥15 letters on a logarithmic visual acuity chart (19). Because patients with inactive uveitis were enrolled in VISUAL II and, therefore, persistent inflammation was not an issue, VISUAL II researchers defined relapse in a manner similar to that used in VISUAL I after 6 weeks (20). Both trials demonstrated efficacy for adalimumab. In VISUAL I, the hazard ratio (HR) for relapse with adalimumab was 0.50 (95% CI: 0.36, 0.70; $P < 0.001$), and in VISUAL II the HR for relapse was 0.57 (95% CI: 0.39, 0.84; $P = 0.004$) (19, 20). The result of these 2 trials was FDA approval a uveitis indication. The inclusion of new chorioretinal lesions as part of the definition of the primary outcome enabled these trials to capture relapse in those diseases for which anterior chamber inflammation or vitritis might not be a good measure of uveitis activity.

Adalimumab also was evaluated as a second immunosuppressive agent for patients with juvenile idiopathic arthritis–associated chronic anterior uveitis already being treated with methotrexate in the Randomized Controlled Trial of the Clinical Effectiveness, Safety and Cost Effectiveness of Adalimumab in Combination With Methotrexate for the Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis (SYCAMORE) Trial (21). Participants were randomly assigned to either adalimumab or placebo, and the primary outcome was the time to uveitis relapse. In juvenile idiopathic arthritis–associated chronic anterior uveitis, anterior chamber cells are a good measure of activity, and vitritis typically is not present. For this trial, relapse was defined as a ≥2-step increase in anterior chamber cells or ≥ 3+ anterior chamber cells on 2 consecutive visits (persistent inflammation near the scale ceiling) or

Table 2. Percentage of Patients With Vitreous Haze Grades at or Above Semiquantitative Scale Thresholds in Patients With Selected Noninfectious Intermediate, Posterior, and Panuveitides in the Standardization of Uveitis Nomenclature Database

Disease (Reference No.)	≥2+ Vitreous Haze, %	≥1+ Vitreous Haze, %
Multiple sclerosis–associated intermediate uveitis (70)	28	70
Pars planitis (71)	27	34
Intermediate uveitis, non–pars planitis type (72)	22	55
Sarcoidosis-associated intermediate uveitis (73)	8	37
Birdshot chorioretinitis (74)	11	32
Multifocal choroiditis with panuveitis (75)	11	27
Punctate inner choroiditis (76)	0	0
Serpiginous choroiditis (77)	0	1
Sarcoidosis-associated posterior uveitis (78)	8	41
Behçet disease uveitis (78)	26	46
Sympathetic ophthalmia (79)	17	32
Early-stage Vogt-Koyanagi-Harada disease (80)	3	19
Late-stage Vogt-Koyanagi-Harada disease (80)	8	17
Sarcoidosis-associated panuveitis (73)	14	42

the new occurrence of worsening of an associated condition (Table 1). Adalimumab was superior to placebo; the HR for relapse was 0.25 (95% CI: 0.12, 0.49; $P = 0.002$) (21). This trial benefited from the inclusion of participants with a single disease for which there was an accepted measure of disease activity.

The Randomized, Double-Masked, Placebo-Controlled Study of the Efficacy of Gevokizumab in the Treatment of Patients With Behçet's Disease Uveitis (Phase III) (EYEGUARD B) Trial (Table 1) also was a single-disease trial; researchers evaluated gevokizumab for the treatment of Behçet disease uveitis with involvement of the vitreous and/or retina (63). Gevokizumab is a monoclonal antibody to interleukin-1β, administered subcutaneously. Participants were randomly assigned to receive gevokizumab or placebo. The primary outcome was time to relapse; relapse was defined as any of the following: 1) a ≥2-step increase in anterior chamber cells or vitreous haze or an increase to 4+; 2) a ≥15 letter decrease in visual acuity; or 3) new retinal infiltrates or acute retinal vasculitis. Unlike many trials in which participants with multiple diseases were enrolled and in which a simple measure was used, this trial defined the primary outcome to reflect the clinical features of Behçet disease uveitis. Unfortunately, gevokizumab was not effective in this trial; the HR for relapse was 0.85 (95% CI: 0.41, 1.77; $P = 0.66$) (63).

The MUST Trial was a comparative effectiveness trial in which participants were randomly assigned to received either the intravitreal fluocinolone acetonide 0.59 mg implant (Retisert, Bausch & Lomb, Bridgewater, New Jersey), which was designed to last 3 years; or systemic therapy with oral corticosteroids and immunosuppression. The primary outcome was not uveitis control but, instead, change in visual acuity. Reasons for this choice of primary outcome included 1) the expected increase in ocular complications, such as cataract and glaucoma, that could affect vision, with the fluocinolone acetonide implant; 2) the hypothesized better control of uveitis with the implant, which could result in better visual outcomes; 3) the uncertainty concerning which trend would result in better long-term visual outcomes; and 4) the importance in visual acuity to patients (32, 33, 64). Visual acuity was measured using logarithmic visual acuity charts, which have a constant relationship between the lines of acuity (unlike the more familiar Snellen acuity charts) (65, 66). A decrease of 3 lines of visual acuity (i.e., 15 letters) represents a doubling of the visual angle (e.g., 20/25 to 20/50), and a 3-line change traditionally has been an outcome used in ophthalmology clinical trials. However, mean change in acuity (i.e., the number of letters read correctly) represents a more efficient measure of change in acuity (67), which was the outcome used in the MUST Trial. The MUST Follow-up Study extended follow-up from 2 to 7 years. At 2 years, there was no significant difference between the 2 treatment groups in change in visual acuity, but at 7 years, participants in the systemic treatment group had gained a mean of 1 letter, whereas those in the implant group had lost a mean of 6 letters; the difference in mean change in visual acuity was 7 letters ($P = 0.006$), favoring systemic therapy. At 7 years, blindness occurred in 22% of the implant eyes versus 13% of the systemic-treatment eyes ($P = 0.04$). Although there were the expected greater rates of cataract and glaucoma with the implant, the difference in visual acuity outcomes appeared to be due to a greater rate of chorioretinal scars and lesions in the implant group occurring in the context of uveitis relapse (33). In general, the risks of systemic corticosteroid or immunosuppressive side effects were not increased with systemic therapy versus those seen in the regional therapy. The only significant difference in systemic side effects was a greater use of antibiotics for infection in

the systemic treatment group (72% vs. 57%; $P = 0.015$) (32, 33).

Two clinical trials have addressed the treatment of uveitic macular edema, the Periocular Versus Intravitreal Corticosteroids for Uveitic Macular Edema (POINT) Trial and the Suprachoroidal Injection of CLS-TA [Triamcinolone Acetonide Injectable Suspension] in Subjects With Macular Edema Associated With Noninfectious Uveitis (PEACHTREE) Trial. Macular edema can be detected on fluorescein angiography or OCT, the former demonstrating vascular leakage and the latter thickening of the macula and intraretinal fluid (49). Because visual acuity correlates better with macular thickness than with amount of fluorescein leakage, change in macular thickness (assessed as the central subfield thickness) on OCT typically is used as an outcome measure in studies of uveitic macular edema (48–50, 68). Improvement in macular edema can be measured as the decrease in thickness (e.g., –100 μm), but this approach should require that all clinical centers in a study use OCT machines with the same normal range. Alternatively, a percentage decrease in thickness (or a ratio of thicknesses) can be used to address the use of different machines from different manufacturers with different normal ranges in multicenter trials (50, 68). Categorical variable outcomes for evaluation of macular edema include resolution (normalization of macular thickness) and improvement (a $\geq$ 20% decrease in macular thickness) (50); the latter threshold was chosen because it correlates better with improvement in visual acuity (50).

In the POINT Trial (Table 1), participants with uveitic macular edema were randomly assigned to 1 of 3 commonly used clinical approaches to injected regional corticosteroid therapy for uveitic macular edema: periocular triamcinolone acetonide 40 mg, intravitreal triamcinolone acetonide 4 mg, or the 0.7-mg intravitreal dexamethasone implant. The ratio of the macular thickness at 8 weeks follow-up to baseline thickness was used as the primary outcome measure of the trial, and the ratio of these ratios then was used for comparison among treatment groups. The ratios of ratios were as follows: intravitreal triamcinolone versus periocular triamcinolone, 0.79 (99.87% CI: 0.65, 0.96; $P < 0.001$); intravitreal dexamethasone implant versus periocular triamcinolone, 0.69 (99.87%: CI: 0.56, 0.86; $P < 0.001$); and intravitreal dexamethasone implant versus intravitreal triamcinolone, 0.88 (99.87% CI: 0.71, 1.08). Intravitreal triamcinolone and the intravitreal dexamethasone implant also were superior to periocular triamcinolone in the secondary outcomes of improvement in and resolution of macular edema and in improving visual acuity (68). For visual acuity, each intravitreal-injection group had an improvement of 5 letters more in mean acuity than did the periocular triamcinolone acetonide group (for intravitreal triamcinolone, $P = 0.003$; for intravitreal dexamethasone implant, $P = 0.004$) at the 8-week visit. The data suggested that both intravitreal injection therapies were superior to periocular injections and that the intravitreal dexamethasone implant was noninferior to intravitreal triamcinolone.

The PEACHTREE Trial (Table 1) was conducted to evaluate suprachoroidal injections of triamcinolone acetonide 4 mg for the treatment of uveitic macular edema. Participants were randomly assigned to suprachoroidal triamcinolone or sham injection. The primary outcome was the proportion of eyes with a $\geq$ 15-letter improvement in visual acuity on a logarithmic visual acuity chart. In the suprachoroidal-injection group, 47% of participants gained $\geq$15 letters of acuity, compared with 16% in the sham injection group ($P < 0.001$) (46). A secondary outcome was improvement in macular thickness on OCT, and the results paralleled the visual acuity results. The mean reduction in macular thickness in the suprachoroidal injection group was 153 μm, compared with 18 μm in the sham injection group ($P < 0.001$) (46). Taken together, these 2 trials suggest that for uveitic macular edema, the anatomic outcome of improvement in macular thickness and the functional outcome of improvement in visual acuity parallel each other, and that either outcome could be used as a primary outcome in short-term studies.

OUTCOME MEASURES FOR CLINICAL TRIALS IN THE FIELD OF UVEITIS

For studies of NIIPPU treatment, especially shorter-term studies, visual acuity has several limitations as a primary outcome. Visual impairment generally is due to the structural complications of the uveitis, such as cataract, macular edema, or choroidal neovascularization (2). Acuity can be improved through treatment of these complications (e.g., cataract surgery, adjunctive regional corticosteroid injections for macular edema, anti–vascular endothelial growth factor injections for neovascularization) but may decline again due recurrences of macular edema or choroidal neovascularization (69). Cataract progression (and the attendant loss of acuity) may reflect either ongoing uveitis activity or the intensity of corticosteroid therapy. In the MUST Trial and Follow-up Study, visual acuity was the primary outcome because of the uncertainty about the relative merits of better initial control of the uveitis with the fluocinolone acetonide implant (with the potential for better acuity outcomes) and the expected greater rate of ocular structural complications with the implant (e.g., cataract, glaucoma) and because it was planned as a longer-term study (64). Visual acuities diverged only after 6 years of follow-up, and in the systemic treatment group, a mean visual acuity of approximately 20/40 was preserved for 7 years (32, 33). These considerations suggest that visual acuity and/or change in visual acuity may be a good outcome measure for some uveitis-related clinical trials, such as comparative effectiveness trials addressing the clinical question of which treatment produces better long-term visual outcomes (e.g., the MUST Trial and Follow-up Study), and trials of treatments for structural complications of uveitis, such as cataract or macular edema (e.g., the PEACHTREE Trial). However, for shorter-term trials evaluating uveitis control, visual acuity and change in visual acuity may be relatively insensitive measures that are indirectly related to uveitis control.

What, then, are good outcome measures for clinical trials of NIIPPU? Vitreous haze appears to be a reasonable outcome measure for trials of intermediate uveitides (e.g., the HURON Trial), and possible outcomes include grade

0 vitreous haze (i.e., inactive disease) and improvement in vitreous haze (e.g., a ≥ 2-step improvement). However, for trials in which participants with several diseases are enrolled, those using this outcome measure have largely shown no benefit for the investigational treatment, even when, as in the case of the SATURN Trial, secondary outcomes suggested benefit. Substantial vitritis (measured by vitreous haze) is not a prominent feature of most cases of posterior and panuveitides (Table 2) (70–80). This problem particularly affects trials in which improvement in vitreous haze was used as an outcome and required >1+ vitreous haze as an enrollment criterion. Recruitment may become difficult, and because the evaluation of vitreous haze has a subjective component (the investigator compares their examination with standard photographs), the stage potentially is set for inadvertent overestimation of vitreous haze at enrollment (to meet recruitment goals) and subsequent regression to the mean in the evaluation of vitreous haze, thereby overestimating treatment effect in the control group and reducing any treatment differences.

Trials in which composite definitions of active or inactive uveitis were used have fared better. The VISUAL Trials included new chorioretinal lesions and a ≥ 15-letter decrease in visual acuity, with increases in anterior chamber cells or vitreous haze as part of the definition of relapse. The trial of the fluocinolone acetonide insert used additional corticosteroids and/or immunosuppressive drugs as well as an increase in vitreous haze. Parenthetically, the limitations of vitreous haze as an outcome are highlighted by this trial, because the majority of relapse events were not due to an increase in vitreous haze. However, because visual acuity may not be a good measure of uveitis activity, its inclusion in composite definitions of uveitis activity may not be optimal.

One potential outcome measure for clinical trials involving corticosteroid-sparing immunosuppressive drugs for uveitis treatment is successful corticosteroid sparing (e.g., inactive disease and prednisone ≤7.5 mg/day). Inactive disease is chosen because data suggest that inactive uveitis is associated with better long-term visual outcomes. The prednisone dose is chosen because data suggested a minimal risk of corticosteroid side effects when the dose is successfully tapered to that level (15, 30, 32, 33).

The First-Line Antimetabolites as Steroid-Sparing Treatment (FAST) Uveitis Trial (Table 1) used this outcome. Antimetabolites are the most commonly used immunosuppressive drugs for corticosteroid sparing in uveitis treatment, and the 2 most commonly used are methotrexate and mycophenolate (15, 32). Results of retrospective studies and analyses in which marginal structural models were used suggested that mycophenolate might be a faster or possibly better corticosteroid-sparing antimetabolite (81, 82). However, in these retrospective studies, researchers used a dose-escalation approach, which is typical in clinical practice, namely starting at the minimally effective dose, then escalating as needed to the maximum dose. Participants in the FAST Trial received an initial dose of each drug for 2 weeks so tolerability could be assessed, then treatment was escalated to the maximum oral dose: 25 mg/week for methotrexate and 3 g/day for mycophenolate (83). In the FAST Trial, methotrexate was noninferior to mycophenolate (for treatment success for methotrexate vs. mycophenolate, OR = 1.5, 95% CI: 0.81, 2.81; $P = 0.20$) (83–85). The trial used a composite definition for inactive uveitis: ≤0.5+ anterior chamber cells, ≤0.5+ vitreous haze, and no active chorioretinal lesions (but without specifying how active chorioretinal lesions were assessed) (83).

One of the problems with specifying definitions for inactive chorioretinitides or panuveitides with chorioretinal or retinal vasculitic involvement is the differential testing required to assess activity for the different diseases (49, 51–53). Fundus autofluorescence is useful for assessing activity for many but not all of the choroiditides, fluorescein angiography is useful for assessing retinal vascular diseases but not for activity of choroidal disease, and OCT is useful for evaluating exudative detachments, as in Vogt-Koyanagi-Harada disease. However, mandating all of these tests for all participants, when some tests would not be used clinically, would impose a testing burden on participants, with the attendant risks of decreased enrollment and decreased adherence to follow-up.

A POTENTIAL APPROACH TO ENROLLING MULTIPLE DISEASES TREATED WITH THE SAME TREATMENT APPROACH IN A TRIAL

One potential solution to the problem of enrolling patients with multiple diseases is the use of a single outcome (e.g., inactive uveitis) but a disease-specific assessment of the outcome. This approach is being piloted in the Adalimumab Versus Conventional Immunosuppression (ADVISE) Trial. The ADVISE Trial is a comparative effectiveness trial comparing adalimumab versus conventional immunosuppression with antimetabolites and/or calcineurin inhibitors for treatment of NIIPPU. In the VISUAL I and II Trials, researchers used a rapid taper and discontinuation of prednisone, which permitted the evaluation of adalimumab's efficacy, because of the greater occurrence of relapses in the placebo group (19, 20). This approach does not mimic clinical care, in which prednisone is tapered relatively rapidly to 7.5 mg/day and then more slowly less than that (15). Furthermore, although VISUAL I and II demonstrated the efficacy of adalimumab for NIIPPU, they did not provide data on the comparative efficacy versus conventional, nonbiologic, immunosuppressive drugs. Preliminary data suggest that adalimumab may be more successful at corticosteroid sparing than are conventional immunosuppressive drugs (34–39, 86). Eligible patients for the ADVISE Trial include patients with NIIPPU except for multiple sclerosis–associated intermediate uveitis and Behçet disease uveitis, because anti–TNF-α agents worsen multiple sclerosis and Behçet disease uveitis appears to be better treated with a regimen including anti–TNF-α agents (22, 27). Participants are stratified on the basis of the pre-enrollment use of no or 1 immunosuppressive drug and the anticipated initial dose of prednisone, and are randomly assigned to either adalimumab or conventional immunosuppression with an antimetabolite and/or a calcineurin inhibitor. The primary outcome is successful corticosteroid sparing by 6 months or follow-up. Successful corticosteroid sparing is defined

Table 3. Visit Testing Schedule in the Adalimumab Versus Conventional Immunosuppression (ADVISE) Trial

Visit Month	Baseline	1	2	3	4	5	6	8	10	12
All Patients Testing										
Medical, ophthalmic, and treatment history	X	X	X	X	X	X	X	X	X	X
Best corrected visual acuity on logarithmic visual acuity chart	X	X	X	X	X	X	X	X	X	X
Complete eye examination[a]	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography	X			X			X			X
Color retinal photographs	X						X			X
Quality-of-life instruments[b]	X						X			X
Complete blood cell count and comprehensive metabolic panel	X	X	X	X	X	X	X	X	X	X
Pre-immunosuppression blood tests for selected infections[c]	X									
Disease-Specific Testing										
Intermediate uveitis[d]: magnetic resonance imaging of the brain	X									
Birdshot chorioretinitis: central and peripheral visual fields	X	X	X	X	X	X	X	X	X	X
Chorioditides except birdshot chorioretinitis[e]: fundus autofluorescence	X	X	X	X	X	X	X	X	X	X
Retinal vasculitides[f]: fluorescein angiography	X	X	X	X	X	X	X	X	X	X
Early-stage Vogt-Koyanagi-Harada disease: optical coherence tomography	X	X	X	X	X	X	X	X	X	X
Late-stage Vogt-Koyanagi-Harada disease: fundus autofluorescence	X	X	X	X	X	X	X	X	X	X

Data from the Adalimumab Versus Conventional Immunosuppression (ADVISE) Trial protocol (87).

[a] Includes slit lamp examination, measurement intraocular pressure, and fundus examination through a dilated pupil.

[b] Includes Euro-QOL, 36-Item Short-Form Survey, and National Education Institute Visual Function Questionnaire.

[c] Includes interferon-γ release assay for tuberculosis, hepatitis B surface antigen, and hepatitis C antibody.

[d] Includes pars planitis and undifferentiated intermediate uveitis to exclude multiple sclerosis (which is worsened by anti-TNF therapy).

[e] Includes multifocal choroiditis with panuveitis, punctate inner choroiditis, serpiginous choroiditis, relentless placoid choroiditis, sarcoidosis-associated choroiditis, undifferentiated choroiditis, and undifferentiated panuveitis with choroiditis.

[f] Includes Behçet disease uveitis, undifferentiated retinal vasculitis, and undifferentiated panuveitis with retinal vasculitis.

as prednisone $\leq$7.5 mg/day for 2 consecutive visits $\geq$28 days apart and inactive uveitis. There are guidelines for the definition of inactive uveitis that are disease specific, and testing is tailored to the specific uveitic disease (Table 3). The consequence of this approach is that there is a core set of tests performed on all participants and a disease-specific set of tests performed on disease-based subsets of participants, with tests used clinically to assess activity. The reasons for this approach include 1) the prevalence and incidence of the individual diseases make a disease-specific trial(s) difficult if not impossible to enroll participants; 2) in clinical practice, all of the diseases enrolled would be treated with the same treatment approaches used in the trial; 3) disease-based subset testing with disease-specific tests limits the testing burden on participants and mimics clinical care; and 4) the primary outcome is the same for all participants, namely successful corticosteroid sparing, and what is individualized is how inactive uveitis is assessed. This approach appears to address the limitation of several previous trials in that it does not rely on a single or limited set of measures not fully applicable to all participants, it uses clinically relevant definitions of inactive disease, and does not include measures with indirect relationship to uveitis activity, such as visual acuity.

Because of the differential administration and dosing of the drugs used in the ADVISE Trial, treatment is not masked. Because of the need to make real-time decisions in treatment management, the assessment of activity is made by the clinical center investigator. To minimize the potential for bias and improve adherence to the treatment protocols, a medical therapy quality assurance committee of experienced clinicians not involved in the recruitment or treatment of patients is used. Images used in assessment of uveitis activity are forwarded from the clinical centers to a centralized image-reading center, whose personnel grade the images in a masked fashion and independently of the clinical center investigator (because of delays in reading-center processing and grading, centralized determination of activity is not logistically feasible). The reading-center grades are compared with those of the clinical center investigators, and discrepancies are forwarded to the medical therapy quality assurance committee for adjudication and corrective action. In addition, to improve adherence to the protocol, the first 2 participants at each clinical center are automatically reviewed by the medical therapy quality assurance committee.

There are potential concerns about this approach. Although available evidence does not indicate a differential

treatment response by disease, if there were disease-specific differential responses for several diseases and an imbalance in these diseases between the 2 treatment groups in a trial, the results could be confounded. Given the number of uveitic diseases, subgroup analyses might not detect disease-specific differential responses, because of the limited power in each disease subset. The disease-specific tests selected were derived from available clinical data and chosen via consensus, but in certain diseases (e.g., birdshot chorioretinitis), the tests selected do not have universal agreement, and future trials might use a different set of disease-specific tests for some diseases. Finally, this approach introduces complexity into the design and conduct of the trial, which makes protocol adherence more difficult.

Although this approach of disease-specific testing and guidelines for assessing inactive disease has been developed for the uveitides, it may be applicable to other situations where disease frequency, activity assessment, and treatment protocols suggest that a trial enrolling several related diseases might be needed. Nevertheless, determination of the value of this approach is needed, and its performance in the ADVISE and other such trials is awaited.

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